9 in 2005 to 6 out of 6 in 2007. This includes today's and tomorrow's presentations. And you will here Dr. Duggirala presenting today on behalf of the Epidemiology Branch.

And this is our vision. To conclude, I just would like to say that, you know, we would like to see that all important post-market questions are addressed by post-approval studies, that studies are realistic and founded on good science.

We would like also studies to be timely, accurate, and provide useful information, based on which we might base some of the regulatory actions if needed.

Also, we certainly would like to have reports that are clearly identified and effectively track. And we are committed to keep our stakeholders apprised.

I cannot stress enough how important it is for us to maintain and cultivate our cooperation with our pre-market colleagues because they are the technical

experts for the product. And we bring the epidemiologic expertise in the study design.

If we proactively address all of these issues in a timely fashion during pre-market, we predict that we will have less enforcement options.

Just for your information, this is the Epidemiology Branch. And the current staff that is involved in cardiovascular devices are marked in blue. You will see there are three epidemiologists, one team leader, a branch chief, and the three project managers that handle post-approval study commitments with regard to cardiovascular devices.

Again, the post-approval studies transformation, vision, and goals present high expectations of us and of the stakeholders. Heightened expectations often bring heightened concerns about burdens, workload, perceived fairness, and added value. It is up to us and our stakeholder to discuss them openly,

responsibly, and collaboratively.

We understand the concerns, but we have to put them into larger contexts of asking and answering the right post-market questions. We welcome an exchange of ideas on diverse methodologies that may be cost-effective, innovative, and productive. We value all analytical approaches and data sources that will give us high-quality answers to the right post-market questions.

Thank you.

CHAIRPERSON YANCY: Thank you very much. Obviously this information is important as increasingly we rely upon the repository of information from post-marketing studies to help us understand the impact of the technologies that we are considering.

Are there any questions for the speaker that you just heard?

(No response.)

CHAIRPERSON YANCY: Great.

1ST OPEN PUBLIC HEARING

CHAIRPERSON YANCY: We will now proceed with the open public hearing portion of this meeting. Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making.

To ensure such transparency of the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of any individual's presentation.

For this reason, FDA encourages you, the open public hearing, our industry speaker, at the beginning of your written and oral statements to advise the Committee of any financial relationship that you may have with the sponsor; its product; and, if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

There is no one that has signed up for this session. However, if there is anyone in the audience who would like to speak, we would appreciate hearing from you.

(No response.)

CHAIRPERSON YANCY: Since no one is coming forward, we will proceed with today's agenda. Please note there will be a second opportunity as there is another open public session in the afternoon.

We will now proceed to the sponsor presentation. Whomever speaks first, if you can help me with the nomenclature, that would be great, the XIENCE V Everolimus-Eluting Coronary Stent System.

I would like to remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

We will begin with the sponsor presentation. Thank you.

MR. JOHNSON: Thank you, Mr. Chairman.

SPONSOR PRESENTATION

MR. JOHNSON: The proper name is the XIENCE V Everolimus-Eluting Coronary Stent.

CHAIRPERSON YANCY: Thank you.

MR. JOHNSON: Sure. Good morning. My name is Gary Johnson. I am Vice President of Regulatory Affairs, Clinical Research, and Quality Assurance for Abbott Vascular.

And on behalf of the employees of Abbott Vascular, our physician investigators, and the patients enrolled in our clinical studies, I would like to thank the panel

members and the Food and Drug Administration for this opportunity to present the XIENCE V Everolimus-Eluting Coronary Stent program.

During today's presentation, we will cover a number of topics. First, I will do a brief introduction. Then Dr. Murthy Simhambhatla from Abbott will review XIENCE V design goals.

Dr. Leslie Coleman from Abbott will summarize our preclinical animal studies. Then Dr. Gregg Stone from Columbia University, who is the PI of the SPIRIT III clinical trial, will review the results of three randomized clinical trials: SPIRIT FIRST, SPIRIT II, and SPIRIT III.

Dr. Stone will be followed by Dr. Mitchell Krucoff from Duke University, who is the co-PI for XIENCE V U.S.A. post-approval clinical study. He will review a combined safety analysis and our integrated post-approval clinical strategy. Finally, Dr. Krishna Sudhir from Abbott will close and

summarize our presentation today.

In addition to the presenters, we also have several consultants with us today: Professor Stuart Pocock from the London School of Hygiene and Tropical Medicine; Dr. Alexandra Lansky from CRF, who served as the angiographic core laboratory; Dr. Peter Fitzgerald from Stanford University, who served as the IVUS core laboratory; and Dr. Renu Virmani from CVPath International. We also have Mr. Ron Van Valen with us from Novartis today.

The purpose of our presentation today is fourfold. First, we want to review XIENCE V design goals and provide a detailed understanding of the major design characteristics and why they were selected.

Second, we want to review the breadth and depth of our preclinical animal studies and vessel healing evaluations. Third, we want to demonstrate the XIENCE V clinical data in its totality establishes a

reasonable assurance of safety and effectiveness based on valid scientific evidence.

And, finally, we want to review the XIENCE V post-approval clinical strategy that augments our pre-approval clinical data and is effectively powered to evaluate low-frequency events.

We are seeking an indication for XIENCE V which is consistent with other drug-eluting stents. The proposed indication is for improving coronary lumenal diameter in patients with symptomatic heart disease due to de novo native coronary artery lesions with lengths less than or equal to 28 millimeters and with reference vessel diameters of 2.5 millimeters to 4.25 millimeters.

We are seeking approval for five diameters of stents, 2.5, 2.75, 3.0, 3.5, and 4.0 millimeters. These diameter stents will be available in six lengths: 8, 12, 15, 18, 23, and 28 millimeters. These diameters and

lengths will be available in both a rapid exchange and over the wire delivery system. All stem sizes have consistent drug dose density of 100 micrograms per centimeter2.

There are three major design components of XIENCE V coronary stent system: the stents and delivery system, which are based on the approved Multi-Link VISION and Multi-Link MINI VISION coronary stent systems; the drug matrix, which is a fluorinated copolymer that has previously been approved on other vascular application devices; and the drug, everolimus, which is manufactured by Novartis Corporation.

Everolimus under the brand name Certican has received two approvable letters from FDA for organ transplant indication. Novartis has also granted FDA rights to reference their IND and NDA to support XIENCE V PMA review. XIENCE V stent has received regulatory approval and is currently marketed in 64 countries outside of the United States.

To put our regulatory and clinical activities into perspective, I wanted to provide a brief regulatory history. Abbott Vascular worked collaboratively with FDA in late 2004 and early 2005 to develop a SPIRIT III pivotal clinical trial design.

At the time of initiation at the SPIRIT III clinical trial, in May of 2005, FDA agreed that a trial design and the supporting clinical data from the XIENCE V clinical program would provide adequate assurance of safety and effectiveness for the XIENCE V system.

During that process, FDA reviewed the everolimus safety, pharmacology, toxicology, and ADME studies and identified no concerns. FDA considers everolimus to be a well-characterized and studied drug; therefore, not a new molecular entity, or NME.

Since everolimus was not an NME, the requirement for 2,000 treated patients in clinical studies typically required for a

drug-eluting stent with an NME did not apply to the XIENCE V program.

The XIENCE V's clinical program will be overviewed in detail today. It is a comprehensive, integrated pre-approval and post-approval program that includes over 16,000 patients. It includes four pre-approval clinical studies, for which you will be presented today, and six ongoing or planned clinical studies, which will be reviewed in more detail later in the presentation.

In summary, the pre-approval clinical studies in their totality have demonstrated the following. All the trials have met their pre-specified primary and powered major secondary endpoints. They have demonstrated non-inferiority and superiority in late loss or bare metal stent. They have demonstrated non-inferiority and superiority in late loss over an approved drug-eluting stent. They have also shown non-inferiority

in target vessel failure compared to the TAXUS drug-eluting stent. And, additionally, all of these trials will have long-term follow-up after five years.

The ongoing and planned clinical studies in their totality are designed to include real-world patients, their power to effectively detect low-frequency events of .5 percent, their design to support label expansion to more complex patient subsets. And these studies will also have long-term follow-up after five years.

In addition to our planned analysis, in response to the panel's comments in December, we have also performed a safety subset analysis of all available two-year data from SPIRIT II and SPIRIT III.

Results of this analysis are consistent with the one-year data from SPIRIT II and III as well as the three-year data from SPIRIT FIRST. The results of this will be presented in more detail later in the

presentation.

So, with that brief introduction, I would now like to turn the podium to Dr. Murthy Simhambhatla to review the XIENCE V design.

DR. SIMHAMBHATLA: Good morning. Work on the XIENCE V system began at a time when the first iteration of drug-eluting stents were already on the international market. It was our design objective to develop a second generation drug-eluting stent by integrating well-categorized, well-tested, and proven components into a system capable of assuring a high level of safety, effectiveness, and deliverability.

We made a decision early in the design process to use the Multi-Link VISION and MINI VISION systems as the platform for XIENCE V. The Multi-Link VISION and MINI VISION stents are the number one selling bare metal stents globally and in the United States. This is a proven and well-tested

system.

The Multi-Link VISION stent is flexible and has thin struts, characteristics that we believe are particularly important in a DES era, by assuring a high level of conformability to the coronary vasculature and potentially a greater extent of endothelial cell coverage. The Multi-Link VISION stent is also proven to be highly deliverable, a characteristic that we wish to preserve, even after putting a drug coating on the stent.

A second design objective was to develop a thin, biocompatible drug coating. We felt that a thin coating would minimize the total cross-section of the coated stent strut and that by doing so, you could not only potentially facilitate the extent of endothelialization but also minimize the potential for flow impairment of side branches traversed by the stent struts.

In order to develop a thin biocompatible drug coating, the system had to

be effective at low drug loading. The polymer had to be stable. Particularly in the local in vivo milieu, the coating had to be uniform and conformal to minimize the potential for plated adhesion to the stent surface. And the drug release had to be controlled and compete over time in order to reduce the potential for persistent vascular effects related to the drug. And, finally, the system in totality had to exhibit good hemocompatibility and vascular compatibility.

Shown here are the four components of the XIENCE V system, as previously described. The platform is a Multi-Link VISION stent and stent delivery system. The drug is everolimus. And the drug-carrying matrix is a fluorinated copolymer. I will now discuss each of these components in turn relative to our design objectives.

The Multi-Link VISION stent, which is the platform for XIENCE V, is based on cobalt chromium technology. This technology

allows us to develop thinner struts without compromising radial opacity or radial strength. The thin struts also allow for good flexibility and conformability and in combination with the delivery system result in a low system profile. And, finally, the delivery system itself has been optimized and minimized vessel injury outside a stented segment by reducing the amount of balloon overhang outside the stent.

Shown here are in vitro flow data by Julio Palmaz and his colleagues. These data indicate that the extent of endothelial coverage is related to the barrier to flow. In particular, these data indicate that the extent of endothelial coverage is compromised for obstacle thicknesses exceeding 100 microns. Based on this result, this group postulated that endothelial coverage may be imputed for thicker thin struts.

It is in this context that we believe that the progression toward thinner

thin struts is important. Shown on the left are the scanning electron microscope cross-sections for the first iteration of drug-eluting stents, for which the strut thickness is significantly greater than 100 microns. Shown on the right is the cross-section for XIENCE V stent with a strut thickness of 81 microns.

Also of note is the dark outline of the polymer coating around the bright stent struts. Shown on the left are the outlines for the first iteration of regulating stents where the coating thickness varies from 13 to 20 microns. The coating thickness for the XIENCE V stent, on the other hand, is approximately eight microns.

We tested the deliverability of the XIENCE V system extensively in our synthetic coronary artery models that simulated tortuosity and simulated lesions. In these three-dimensional models, we demonstrated with the deliverability of the XIENCE V system for

the smallest and largest stent sizes were equivalent to the MINI VISION and VISION bare metal stents, respectively.

The drug everolimus is a proliferation signal inhibitor that acts in the late G1 phase of the cell cycle to inhibit cellular proliferation in a reversible manner. Everolimus belongs to the same family of synthetic macrolide compounds as sirolimus. And both these drugs have IC50 values in a similar range for the inhibition of smooth muscle cell proliferation.

We studied a wide range of drug doses in porcine coronary arteries from 100 micrograms per centimeter2 to 800 micrograms per centimeter2. We observed sufficient drug effect at 100 micrograms per square centimeter with no evidence of toxicity of medial necrosis at 800 micrograms per centimeter2.

The lowest effective dose of 100 micrograms per centimeter2 was there for selective clinical development. With this

dose, we had an eight-fold safety margin given the absence of toxicity of medial necrosis with the 800 microgram per centimeter2 dose in our porcine models.

The amount of drug on the XIENCE V stent is significantly reduced relative to other limus-eluting stents. In particular, the amount of drug in the XIENCE V stent is reduced by 41 percent relative to Cypher. This is notable given that the IC50 values for both everolimus and serolimus are in a similar range for the inhibition of full muscle cell proliferation.

We, therefore, achieved a key design objective of effectiveness with reduced drug loading. And this will be demonstrated later in the clinical presentation.

The XIENCE V polymer selection and coating design were optimized for the controlled elution of everolimus over time and for the complete release of drug over time. Approximately 80 percent of the drug is

released by 30 days. And substantially all of the drug is eluted by 820 days.

XIENCE V coating design comprises a primer and matrix system. In the expanded view on the right, the stent strut is shown in white. The drug-carrying fluoropolymer matrix is shown in blue. And a thin primer layer is shown in red. It is the function of the primer to ensure good adhesion between the drug coating and the thin strut.

This system does not have a top coat. In our experience, this system allows for better manufacturing control and drug release than a top coat system for such thin coatings. This system also allowed us to optimize the adhesion of the coating to the stent strut while minimizing unwanted adhesions to the delivery balloon.

The drug-carrying matrix is an ultra pure copolymer comprised of vinylidene fluoride and hexafluoropropylene monomers. This polymer has been used in approved

cardiovascular, neurologic, and ophthalmic sutures.

The ratio of the vinylidene fluoride and hexafluoropropylene allows us to optimize the coating elasticity in order to prevent the coating from cracking upon stent expansion and coating toughness to ensure the durability of the coating during the act of stent delivery to the target lesion.

This polymer is one of the most stable entities chemically because of its durable carbon carbon backbone and the covalent carbon fluorene bonds. And this stability confers to this polymer a high degree of stability in vivo as well as biocompatibility. And, finally, this polymer has good hemocompatibility.

Shown here are micrographs of the XIENCE V system, illustrating its coating integrity. The coating was designed to minimize webbing, bridging, and strut-to-strut contact in the crimped state. It was also

designed to maintain the coating integrity after simulated use, stent expansion, and fatigue testing.

A key design objective for the XIENCE V system was to assure a level of hemocompatibility that was at least equivalent to the bare metal VISION platform. We tested hemocompatibility in accordance to ISO10-993 and showed in an un-hecronized ex vivo shunt study that the amount of polymers accumulated on the XIENCE V stent was less than that on the bare metal VISION stent. We, therefore, surpassed our objective of ensuring equivalent hemocompatibility to the bare metal stent.

We also studied the vascular response of the XIENCE V system and XIENCE V copolymer extensively in porcine models and demonstrated that all the way out to two years, the polymer response is equivalent to the VISION bare metal stent. We have also studied the vascular response of three times the amount of polymer on the stent and have

found the response equivalent to the bare metal vision stent.

So, in summary, the XIENCE V system is built on the proven VISION stent and stent delivery system. The VISION stent is flexible and has thin struts. It is also a deliverable stent.

We have also developed a thin, biocompatible drug coating that is effective at low drug loading. The polymer is stable. The coating is uniform and conformal around the stent struts.

The drug release is well-controlled and complete over time. And, finally, the system exhibits good hemocompatibility and vascular compatibility.

I will now turn over the podium to my preclinical colleague, Dr. Leslie Coleman.

DR. COLEMAN: Good morning. I would like to present to you an overview of the XIENCE V preclinical program. The clinical program consisted of an extensive

assessment of the biocompatibility of the XIENCE V system and assessment and characterization of the pharmacokinetics of XIENCE V, a comprehensive safety assessment, and an assessment of the endothelial cell response to XIENCE V.

The biocompatibility of the XIENCE V system was demonstrated through numerous in vitro and in vivo studies. All studies were conducted in compliance with applicable guidelines, and all studies passed.

The pharmacokinetics of the XIENCE V was characterized in a porcine coronary artery model. And, as you can see in the graph, the graph on the left demonstrates that the XIENCE V released everolimus in a consistent and controlled manner, with complete drug release by 120 days. And we believe that it's very important to have complete release of the drug from the system in order to allow for vessel healing.

These release kinetics translate

into effective arterial delivery, as you can see on the right graph, where we have controlled release of everolimus to the target tissue or the stented artery over time. This has allowed for the presence of everolimus during the first several months following stent implantation consistent with the peak cellular phases of neointimal hyperplasia.

The clinical pharmacokinetics of XIENCE V were studied in several substudies within the SPIRIT II and SPIRIT III clinical trials.

Results from all P-K substudies were consistent across geographies and showed limited systemic exposure of everolimus up to a total dose of 588 micrograms. And at all times the amount of systemic everolimus correlated with the number of stents implanted into the patient.

Importantly, systemic exposure to everolimus was well below the minimal therapeutic blood level of three nanograms per

ml that must be maintained at a steady state when everolimus is delivered orally to prevent organ transplant rejection.

We conducted a comprehensive safety assessment of the XIENCE V system. This entailed 35 animal studies. We evaluated the system in two species. And we have data on the XIENCE V system extending from 28 days out to 2 years.

We chose to evaluate the XIENCE V in two animal species in order to account for any species-specific responses. And we evaluated the XIENCE V system in numerous configurations, including single stents, which we did evaluate in two species, again with data out to two years. We evaluated the response to overlapping XIENCE V stents, also in two species.

And then, as mentioned previously, we conducted studies to understand fully the safety margin of the system by evaluating a maximum dose system that has eight times the

amount of everolimus on the system as well as polymer-only systems, ranging from 1X polymer out to three times the amount of polymer on the system. And we have evaluated these polymer systems out to two years.

From a safety perspective, our goal was to establish effective drug delivery with rapid vessel healing. We defined vessel healing by the following four criteria that we should have a smooth muscle cell rich neointima incorporating all stent struts as rapidly as possible. There should be minimal persistent fibrin, minimal long-term inflammation, and a rapidly endothelialized lumen.

These are representative histologic images of XIENCE V as compared to a VISION bare metal stent at numerous time points from 28 days out to 2 years. The bar graph below demonstrates the inflammatory scores over time, again comparing XIENCE V to VISION metallic stents from 28 days out to 2 years.

Inflammation is scored on a scale of zero to four with a score of zero to one being considered background in this particular model, in the porcine model.

As you can see, the neointimal response to XIENCE was similar to a VISION metallic stent. And there is minimal long-term inflammation. From 180 days out to one year and then to 2 years, the neointimal response is stable.

At higher magnification, one can appreciate the cellular composition of the vessel wall in response to a XIENCE implant. The bar graph demonstrates fibrin over time. And, as we would expect, there is peri-strut fibrin at 28 days consistent with peak drug elution. But as the system elutes the drug, there is minimal to no fibrin consistent with elution of the drug and no longer drug being detected in the tissue. Again, the neointimal response is stable from six months out to two years, consistent with a healed vessel.

Endothelialization in the porcine model was complete at all time points evaluated. To summarize the safety response, during the active phase of drug elution, we did observe that there was a fully endothelialized lumen, there was neointimal coverage of all stent struts with peri-strut fibrin, consistent with drug elution, inflammation comparable to VISION metallic stent and no mineralization, no medial necrosis, demonstrating the overall lack of vessel toxicity.

At 180 days and beyond, the phase at which there is no longer a drug detected in the tissue, the vessels were again fully endothelialized and largely in a quiescent, healed state. And so these findings we believe are consistent with vessel healing.

So, to conclude the safety assessment, we have demonstrated safety in two animal models with data out to two years. We have met the goal of our DES safety program by